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1) Kirkpatrick, Cell. Mol. Life Sci., 55(3):437-449 (March 1999).
2) Kolodner and Marsischky, Curr Opin. Genet. Dev., 9(1):89-96 (Feb. 1999).
3) Chamber et al., Mol. Cell. Biol., 16(11):6110-6120 (Nov. 1996).
4) Hunter et al., EMBO J., 15(7):1726-1733 (April 1, 1996).
5) Richardson et al., Biol. Reprod., 62(3):789-796 (March 2000).
6) Baker et al., Nat. Genet., 13(3):336-342 (July 1996).
7) Hassold, Nat. Genet., 13(3):261-262 (July 1996).
8) Datta et al., PNAS, 94(18):9757-9762 (Sept. 2, 1997).
9) Hunter and Borts, Genes Dev., 11(12):1573-1582 (Jun. 15, 1997).
10) Sniegowski, Curr. Biol., 8(2):R59-61 (Jan. 15, 1998).
11) Jiricny, Mutat. Res., 409(3):107-121 (Dec. 14, 1998).
12) Yamazaki et al., J. Exp. Zool., 286(2):212-218 (Feb. 1, 2000).
13) Prelle et al., Cells Tissues Organs, 165(3-4):220-236 (1999).

Thanks in advance,

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Mismatch repair: **Origin of species?**

Paul Sniegowski

Mismatch repair reverses replication errors and inhibits recombination between diverged sequences. This has been suggested to be important in speciation, especially in prokaryotes, but theoretical analysis indicates that genetic divergence in bacterial populations is not constrained by naturally occurring recombination levels.

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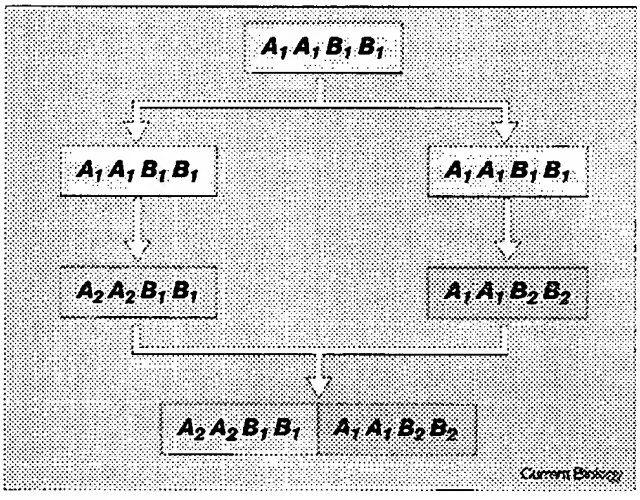
The origin of species, Darwin's 'mystery of mysteries', remains a subject of considerable research interest. We have yet to solve fully the problem of how a continuous process of evolution produces the discontinuous groupings of organisms recognized as species [1]. The classic genetical model for speciation in sexual eukaryotic populations was proposed by Dobzhansky, Mayr and Muller in the 1930s and 1940s [2–4] (Figure 1) and is based upon the 'biological species concept' championed by Mayr. In this view, species are defined as groups of interbreeding populations that are reproductively isolated from other such groups. Barriers to reproduction may be divided into 'prezygotic' and 'postzygotic' isolating mechanisms, which inhibit gene flow by preventing mating between members of different species or by causing hybrid sterility or inviability. Population genetic theory has shown that even very low levels of gene flow can be sufficient to swamp genetic divergence between sexual populations.

Figure 1



A classical allopatric model of speciation [2–4] involving evolution at two loci, *A* and *B*. A single ancestral population (top) fixed for genotype $A_1A_1; B_1B_1$ is divided geographically into two subpopulations. One subpopulation evolves genotype $A_1A_1; B_2B_2$ and the other evolves genotype $A_2A_2; B_1B_1$. When the populations are rejoined, epistatic interactions between the A_2 and B_2 alleles render the hybrids sterile or inviable, and the populations are free to diverge evolutionarily as different species (bottom).

Can the biological species concept be extended to bacteria? That it can has been suggested on the basis of a considerable amount of recent research showing that most bacterial populations are not strictly asexual, but instead undergo recombination in nature at detectable levels [5,6]. On this view, understanding mechanisms of speciation in bacteria would involve knowing what drives bacterial population divergence and what prevents recombination between divergent bacterial genomes in natural populations. A recent paper by Vulic *et al.* [7] proposes that the action of two major pathways of DNA metabolism, the mismatch repair and SOS systems, may hold the "molecular keys to speciation" in bacteria, and perhaps even in eukaryotes as well.

Components of the methyl-directed mismatch repair (MMR) pathway bind to and correct mismatched base pairs shortly after DNA replication, using the transient hemimethylation of newly replicated DNA as the source of information about which strand has been newly synthesized [8]. Activity of the MMR system has also been shown to inhibit recombination between diverged sequences [9]. Three recent papers [7,10,11], including the one by Vulic *et al.* [7], have independently shown that this inhibitory effect on recombination can be modeled as an exponential function of the amount of divergence between two recombining sequences (Figure 2). Because this relationship holds true in enterobacteria [7], *Bacillus* species [10] and yeast [11], it may well be universal at the DNA level.

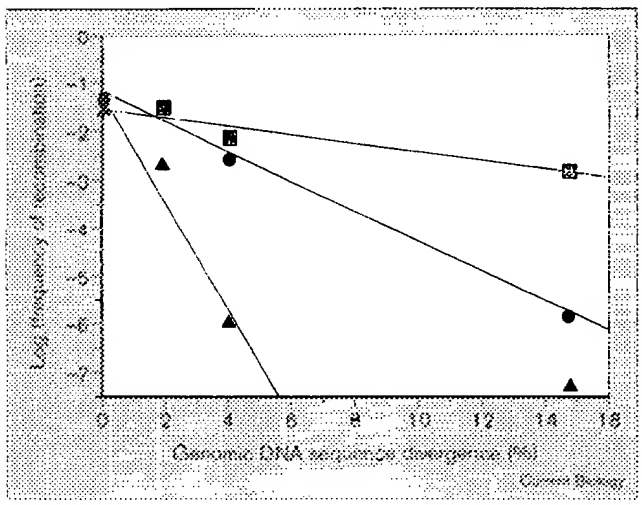
The SOS pathway mediates responses to DNA damage in diverse bacterial species. Although the full details of this system have yet to be elucidated, one of its major effects is clear enough: in response to DNA damage, the SOS system facilitates the bypassing of certain types of DNA lesion which would otherwise prevent replication [12]. SOS-facilitated bypass-replication is error-prone compared with normal DNA replication, and hence it introduces mutations. In addition to its effect on the mutation rate, the SOS system increases the recombination rate between diverged bacterial DNA sequences through the overproduction of RecA, the major protein involved in mediating recombination [9].

Whereas the SOS system clearly is activated in response to metabolic stress, very recent observations cited by Vulic *et al.* [7] suggest that the MMR system is inhibited by stress. Vulic *et al.* [7] therefore propose that stress causes rapid genetic diversification by its combined effects on the rates of point mutation and intragenomic recombination (increased through induction of the SOS system), and on horizontal genetic exchange (increased through inactivation of the MMR system). When the stressful circumstance is over, the SOS system is repressed and MMR is reactivated, decreasing the rates of mutation, rearrangement and horizontal gene transfer and possibly completing a speciation event by making permanent the newly arisen genetic divergence between strains.

The hypothesis of Vulic *et al.* [7] is intriguing because it leaps directly from DNA metabolism to speciation, avoiding thorny issues such as the requirement for geographic isolation and the nature of 'speciation genes' postulated to mediate reproductive isolation, issues that have historically made the study of eukaryotic speciation contentious [1]. Indeed, say Vulic *et al.* [7], "The evolutionary conservation of the key MMR and recombination components encourages the extension of the ideas discussed to the eukaryotic world".

There are some serious problems with this idea, however, even as it applies to prokaryotes. One is that the effects of genetic divergence in laboratory crosses cannot be directly equated to genetic (sexual) isolation between evolving bacterial populations in nature. At least five steps must be completed for a successful recombination event to occur in a natural bacterial population [10]. First, donor DNA must be taken up by the recipient cell. Second, the DNA must escape the recipient's restriction system. Third, the donor and recipient DNA must form a heteroduplex intermediate. Fourth, the heteroduplex must escape the surveillance of the mismatch repair system, which will abort recombination between divergent sequences. And fifth, the donor gene product must function successfully in the recipient genetic background. Although increased sexual isolation between divergent strains in nature could be a consequence of any one of these steps, the hypothesis of Vulic *et al.* [7] takes only one of them — the fourth — into account.

Figure 2



The effects of sequence divergence and MMR activity on recombination in enterobacteria as measured in laboratory experiments [7]. Red circle, wild-type MMR background; blue triangle, genetic background in which MMR proteins MutS and MutL are overexpressed; green square, genetic background deficient in MutS production.

A second problem is that rates of recombination measured in prokaryotes in the laboratory cannot be directly related to those measured in sexually reproducing eukaryotes. In the latter, recombination involves a roughly 50:50 swap between entire genomes and is obligately tied to reproduction at every generation. If an experimenter measures a recombination rate r per generation between two sequences in the laboratory in a sexual species, then it is a good bet that a similar rate r applies in nature. In prokaryotes, however, r must depend in part on the rate at which opportunities for recombination arise in the natural setting, and these are necessarily constrained by the microhabitat distributions of potentially recombining genomes, the availability of vectors that shuttle DNA between cells (where necessary) and other such ecological factors. Indeed, although prokaryotes do have sex, they do not get around to it very often: recombination rates (per gene segment per genome per generation) in nature are estimated at only about 1×10^{-9} for *Escherichia coli* [13] and about 5×10^{-8} for *Bacillus* species [14].

Cohan [14] has analyzed mathematical models of sequence divergence and sexual isolation in bacteria under reasonable assumptions about the relative effects of recombination, mutation, selection and population structure. The main conclusion from his work is that naturally occurring levels of recombination are most probably too low to constrain adaptive divergence of bacterial populations into niche-adapted 'species'. Indeed, Cohan suggests that the biological species concept may not be appropriate for bacteria. If so, then the hypothesis of Vulic *et al.* [7] proposes an answer to a problem that does not exist: the recombination-suppressing activity of the MMR system need not be invoked in order to explain divergence in bacteria, as the recombination rate is already too low to swamp divergence.

Is there a role for the MMR system in eukaryotic speciation? Hunter *et al.* [15] have recently demonstrated that hybrids between the yeast *Saccharomyces cerevisiae* and its

closest known relative *S. paradoxus*, which are typically inviable, show increased viability if MMR activity is lacking. These observations are certainly consistent with the notion that the MMR system creates part of the genetic barrier between eukaryotic species, as these two species show approximately 30% sequence divergence. A key issue, however, is whether the observed MMR effect is a cause of speciation or merely a consequence. That is, is the MMR effect on sexual isolation in yeast observable only because the evolution of reproductive isolation by other means allowed the *S. cerevisiae* and *S. paradoxus* genomes to diverge extensively in the first place? Theoretically, speciation may require divergence in as few as two genes for reproductive isolation to arise [2–4] (Figure 1), and many sexual species are diverged by as little as 2% in their DNA [14] — far below the levels of divergence at which the MMR is observed to affect recombination rates significantly (Figure 2). The origin of species may not be as simple as mismatch repair.

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References

1. Coyne JA: **Genetics and speciation.** *Science* 1992, **355**:511-515.
2. Dobzhansky T: *Genetics and the Origin of Species.* New York: Columbia University Press; 1937.
3. Muller HJ: **Isolating mechanisms, evolution, and temperature.** *Biol Symp* 1942, **6**:71-125.
4. Mayr E: *Systematics and the Origin of Species.* New York: Columbia University Press; 1942.
5. Maynard Smith J: **Do bacteria have population genetics?** In *Population Genetics of Bacteria.* Edited by Baumberg S, Young JPW, Wellington EMH, Saunders JR. Cambridge, UK: Cambridge University Press; 1995.
6. Dykhuizen DE, Green, L: **Recombination in *Escherichia coli* and the definition of biological species.** *J Bacteriol* 1991, **173**:7257-7268.
7. Vulic M, Dionisio F, Taddei F, Radman M: **Molecular keys to speciation: DNA polymorphism and the control of genetic exchange in enterobacteria.** *Proc Natl Acad Sci USA* 1997, **94**:9763-9767.
8. Modrich, P: **Mechanisms and biological effects of mismatch repair.** *Annu Rev Genet* 1991, **25**:229-253.
9. Matic I, Rayssiguier C, Radman M: **Interspecies gene exchange in bacteria: the role of SOS and mismatch repair systems in evolution of species.** *Cell* 1995, **80**:507-515.
10. Majewski J, Cohan F: **The effect of mismatch repair and heteroduplex formation on sexual isolation in *Bacillus*.** *Genetics*, in press.
11. Datta A, Adjiri A, New L, Crouse GF, Jinks-Robertson S: **Mitotic crossovers between diverged sequences are regulated by mismatch repair proteins in *Saccharomyces cerevisiae*.** *Mol Cell Biol* 1996, **16**:1085-1093.
12. Friedberg, EC, Walker, G, Siede, W: DNA *Repair and Mutagenesis.* Washington: American Society for Microbiology Press; 1995.
13. Whittam TS, Ake SE: **Genetic polymorphisms and recombination in natural populations of *Escherichia coli*.** In *Molecular Paleopopulation Biology.* Edited by Takahata N, Clark AG. Tokyo: Japan Scientific Society Press; 1993.
14. Cohan FM: **The effects of rare but promiscuous genetic exchange on evolutionary divergence in prokaryotes.** *Am Nat* 1994, **143**:965-986.
15. Hunter N, Chambers SR, Louis EJ, Borts RH: **The mismatch repair system contributes to meiotic sterility in an interspecific yeast hybrid.** *EMBO J* 1996, **15**:1726-1733.
16. DeSalle R, Hunt J: **Molecular evolution in Hawaiian drosophilids.** *Trends Ecol Evol* 1987, **2**:212-216.